PBPK Modeling of Xylenes

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Why Modeling?

- Previous suggestions from COT to use PBPK modeling in AEGL determinations.
- PBPK models were used to estimate brain and blood concentrations at LC_{50} for various VOCs. They found that some of variation in LC_{50} values was due to toxicokinetics. For 12 of 15 VOCs, the Cv* at the LC_{50} ranged from 2.0 - 9.5 mM, whereas the LC_{50}s ranged from 2,965 - 129,000 ppm (DeJongh et al., 1998).
- The AEGL-2 and -3 key study used 4-h exposure duration: extrapolation to shorter time periods necessary

• Cv = venous blood concentration

Summary of proposed AEGL values for Xylenes					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	130	130	130	130	130
AEGL-2	990	480	430	430	430
AEGL-3	2100	1000	930	930	930

AEGL-1: Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 min. (Hastings et al., 1986)

AEGL-2: Rats exposed to 1300 ppm mixed xylenes for 4 h exhibited poor coordination (Carpenter et al., 1975)

AEGL-3: Rats exposed to 2800 ppm for 4 h exhibited prostration followed by full recovery (Carpenter et al., 1975)

Current 10 and 30 m AEGL-2 and -3 extrapolation:

One compartment model; used NOMEN program
Following assumptions made:

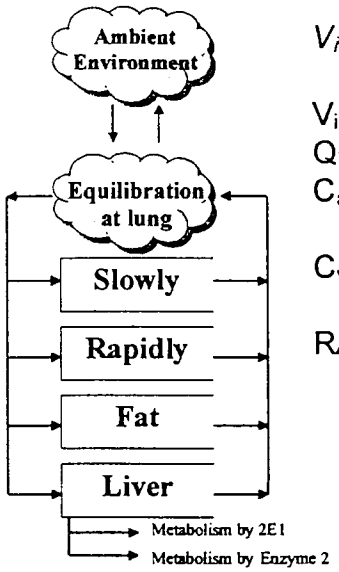
- toxicological endpoint and intensity of toxicological effect should be same as observed after admin. of 430 ppm for 4 h
- it is concentration and not amount of the substance (AUC) responsible for the effect, qualitatively and quantitatively
- data from kinetic studies in human volunteers (see Table 11, page 37) are appropriate for further kinetic calculations
- the data of m-xylene were used to represent the mixture of all xylenes
- the kinetics of m-xylene are linear in the concentration/ dose range which is under consideration.
- assumed inhalation volume and frequency being constant

PBPK Model Specifics:

- Basically only one xylene model published, and it was for the single isomer m-xylene. A series of publications were generated by the Krishnan and Tardif research group, with the main differences among the models being the physiological parameters used.
- We coupled the model with additional human data from four different publications for verification.
- We then ran the rat model to determine Cv (venous blood concentration) for the AEGL endpoint. We next ran the human model for each time period to determine the equivalent exposure producing the same Cv.

What We Used:

- A standard 4 compartment model.
- Tardif, et al., 1993.
  gas-uptake data in rats: 500, 1000, 2000, 4000 ppm
- Tardif et al., 1997.
  Cv in rats following 4 hr exposure to 100 or 200 ppm
- Haddad et al., 1999.
  Added Cv in rats following 4 h exposure to 50 ppm
  Metabolism parameters except as noted
  Partition parameters (from Gargas 1987 et al. (in vitro))
- Tissue flows and volumes are standard parameters values used in modeling, generally from Brown et al.



$V_i dC_i/dt = Q_i(C_a - C_{vi})$ - RAM

Where

V_i = tissue volume (L)

Q_i = tissue perfusion rate (L/h)

C_a = concentration of solvent in the systemic arterial blood (mg/L)

C_{vi} = concentration of solvent in venous blood leaving tissue, i (mg/L)

RAM = rate of change in the amount metabolized

RAM = AMS + AML

$RAMS = V_{max} \times C_{VL}/(K_m + C_{VL})$

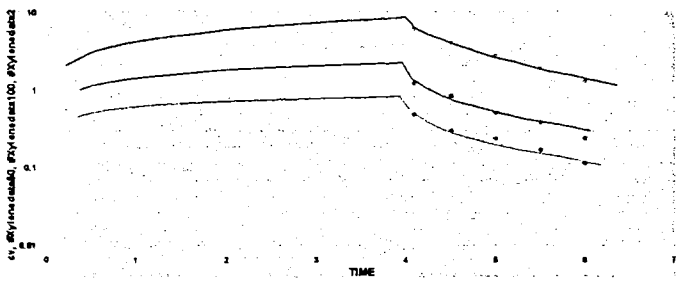
$RAML = KF * C_{VL}$

(KF = 1st order rate constant for high-capacity/low affinity enzymes)

Haddad 1999 Rat Model:

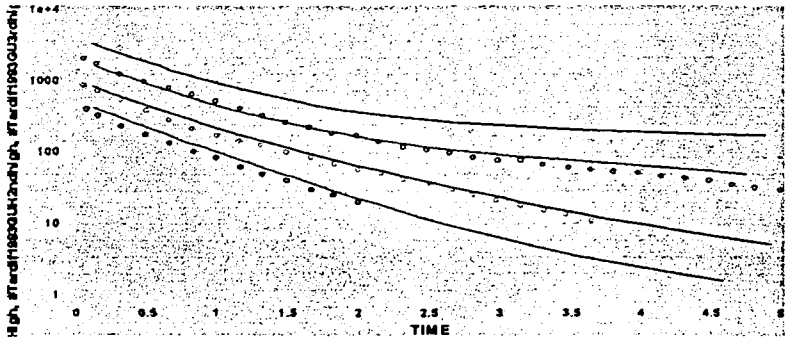
We chose the 1999 model over 1997 model because 1999 model was second version, more data rich, and fit slightly better. Was not a large difference between them.

Does have limitation that was in SD rats and only had post exposure data at xylene concentrations up to 200 ppm.



Model Using Tardif's Gas Uptake Data:

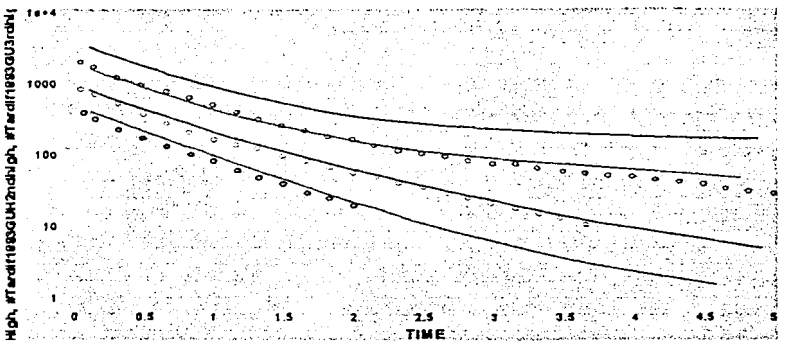
In the Haddad 1999 model, slightly different parameters used for tissue volumes and metabolism compared to Tardif 1993 model. We ran the 1999 model with the 1993 gas uptake data (500, 1000, 2000, 4000 ppm). The results suggest that the 1993 and 1999 models are essentially the same since the plot shown here is essentially the same as in the 1993 paper. At the lower concentrations, the model would actually fit perfectly if they adjust the starting concentration to what shows. Note: acute lethality critical study was at exposure level between the 2nd and 3rd doses here.



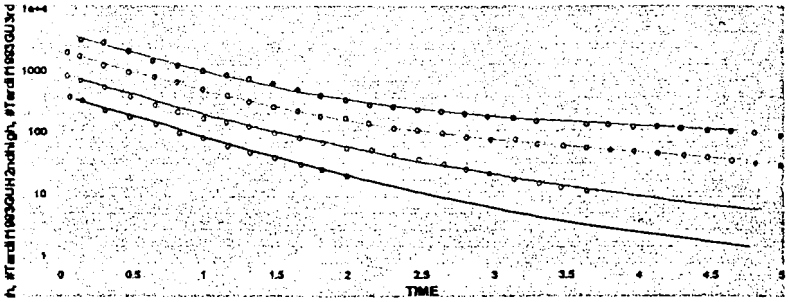
So, using same model, we optimized starting concentrations to reflect first data points.

Also, saw that we needed to include a 2nd pathway of metabolism - (lumped metabolism by all of CYPs other than CYP2E1; account for high capacity/low affinity pathways of metabolism). The metabolism by second series of CYP is given as:
*rate of metabolism (RAM) = KF * C_{VL} where*
*KF = 0.1/BW**0.3*

Added the second pathway and determined KF (1st order rate constant for high-capacity/low affinity enzymes).

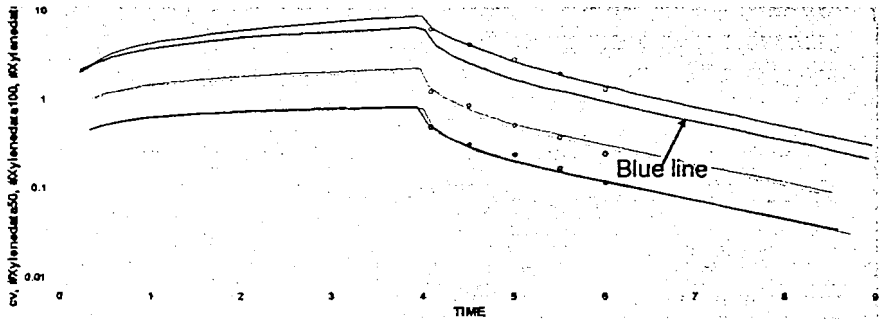


Unchanged from Tardiff paper

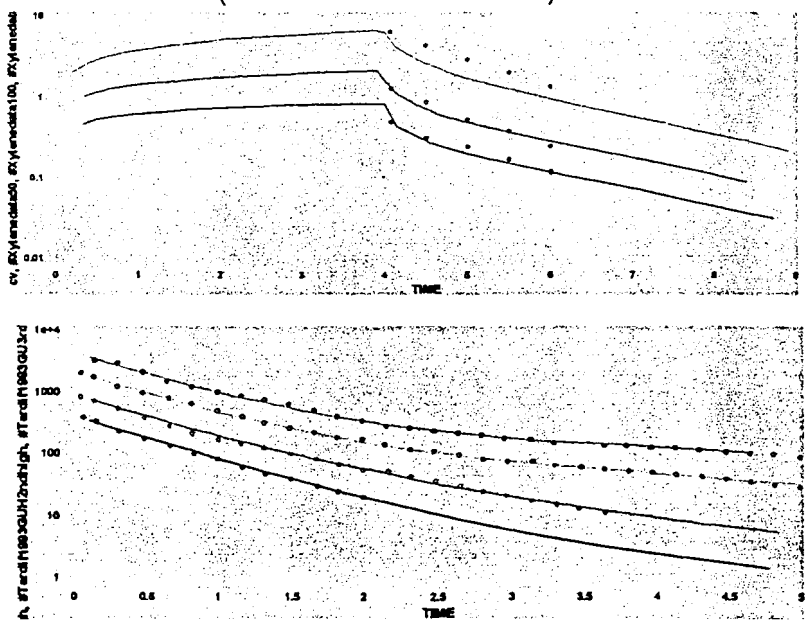


Optimized starting conc.; included 2nd metabolism pathway

Reran the model with all the same parameters against the Haddad data. A good fit is obtained overall, although the 200 ppm is underpredicted a little. However, we are mostly concerned with estimating C_V in rats at very high concentrations (1,000 to 3,000 ppm). This figure shows what the model does without linear pathway (perfect fit) and with it. No real difference at 50, 100 ppm, but the blue line is the new model at 200.

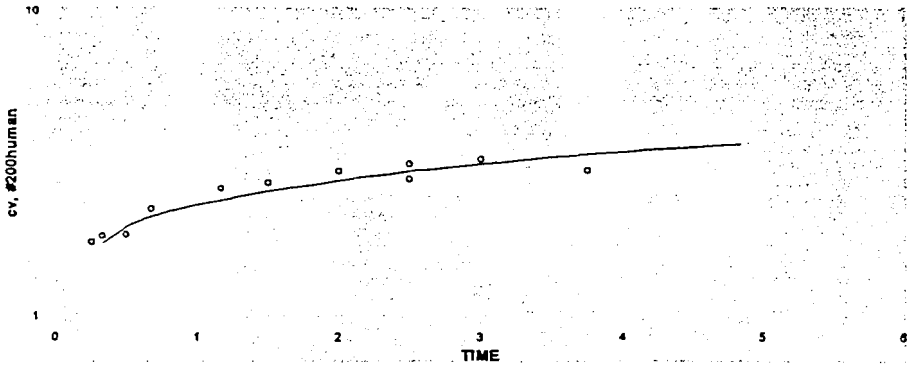


New rat model (with linear metabolism).



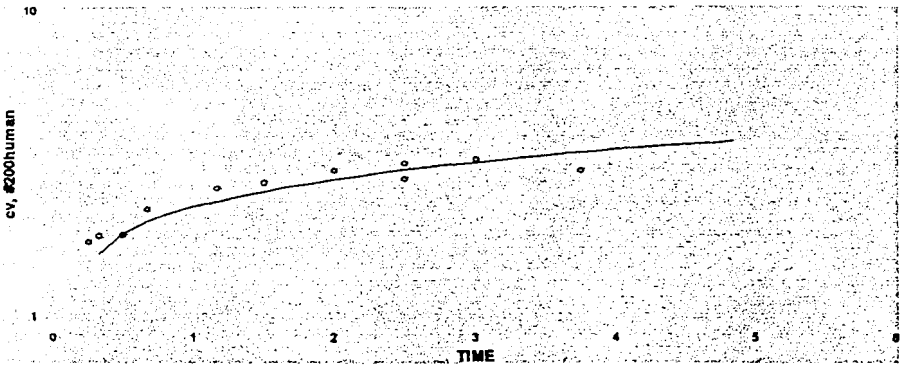
Application of Model to Humans:

200 ppm data sets from multiple papers (human). BW assumed 84.5 kg. The QRC (blood flow to richly perfused) was set at 55% of QC (cardiac output). This model uses Gargas/ Pierce PB (blood: air partition coefficient) of 32 and QFC (blood flow to fat) was then optimized at 10% of QC.



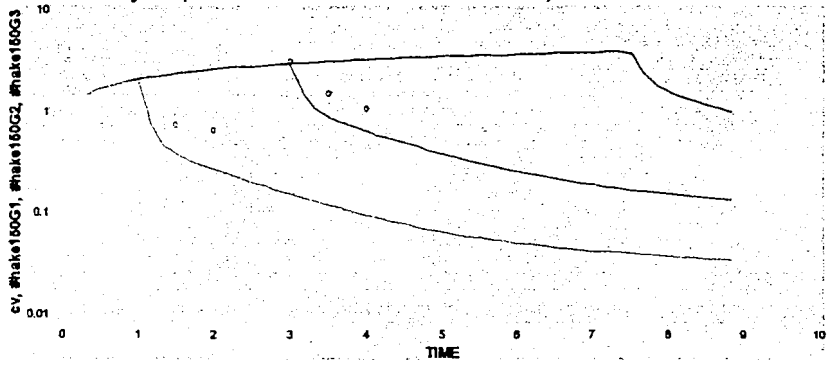
Application of Model to Humans:

If we use Sato's PB (blood: air partition coefficient) of 26.4 instead, we get a better fit with QFC (blood flow to fat) at 8%. The higher PB works better for the early data points.



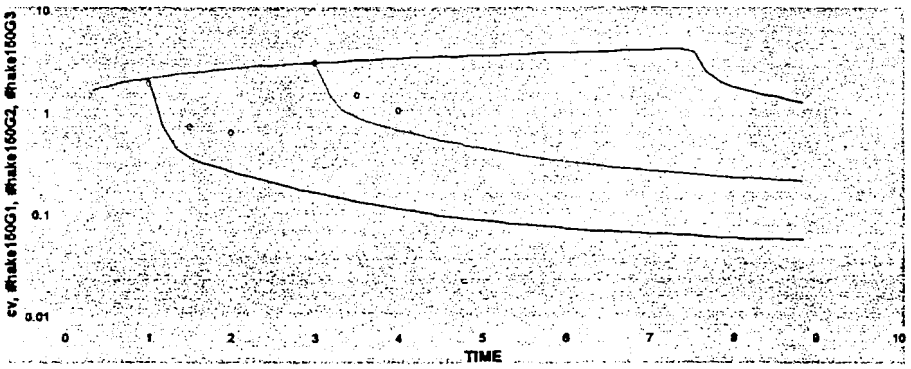
Application of Model to Humans:

Turning to another human dataset (post-exposure blood data by Hake using p-xylene). Measured PBs are 38.5 (Sato/Pierce) and 44.7 (Gargas). If we use the Sato/ Pierce PB, and QFC = .08, best fit the peak blood levels with VmaxC is 5.0 (shown here); if QFC = 0.10, VmaxC appears to be ~ 4 (essentially equivalent to what is shown).



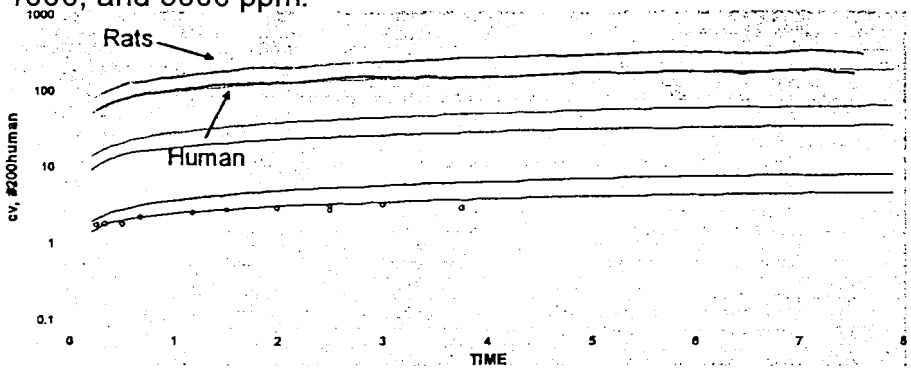
Application of Model to Humans:

Gargas's PB gives essentially same results. Here, PB = 44.7, QFC = 0.1, VmaxC = 4. Thus, while limited data for p-xylene, appears it can be modeled with same parameters as m-xylene except for the expected modification to Vmax. Note: We didn't bother adjusting km too because we don't have data at different exposure levels to work with (practically.)



Comparison of Pharmacokinetics in Rats and Humans:

Rats achieve higher blood concentrations than humans. This is probably mostly due to higher PB measured in rats (46 vs. ~ 26-32 in humans). In this Figure, C_V is plotted for rats and humans using the validated models presented earlier at 200, 1000, and 5000 ppm.



Results of the Model– AEGL-2:

According to this PBPK model, the following exposure concentrations lead to blood concentrations (Cv) equivalent to the rat at 1300 ppm/4 hours (target Cv of 64.2 mg/L)

Duration	low	high	avg	+/-
10 m	7250	9800	8525	15%
30 m	4050	5350	4700	14%
1 h	3280	4150	3715	12%
4 h	2033	2542	2288	11%
8 h	1670	2064	1867	11%

Results of the Model– AEGL-3:

According to this PBPK model, the following exposure concentrations lead to blood concentrations (Cv) equivalent to the rat at 2800 ppm/4 hours (target Cv of 158 mg/L)

Duration	low	high	avg	+/-
10 m	17600	20600	19100	8%
30 m	9850	11200	10525	6%
1 h	7800	9000	8400	7%
4 h	4800	6130	5465	12%
8 h	3970	4975	4473	11%

Effect of work on Cv:

Flow parameters for resting and two work loads:

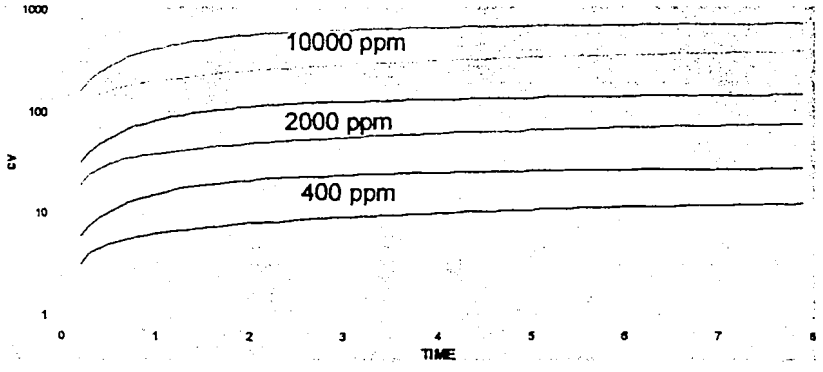
Based on Jonsson (2001): measured QP in five individuals at rest, 50W and 100W;

Johanson (1986): summary of literature values for relative tissue flows to each group at rest, 50W and 100 W.

	QPC	QCC	QLC	QFC	QRC	QSC	Total QFs
Resting, human	18	18	0.26	0.1	0.50	0.14	1.00
50 W, human	53	50	0.13	0.03	0.6	0.24	1.00
100 W, human	87	68.5	0.076	0.03	0.58	0.314	1.00

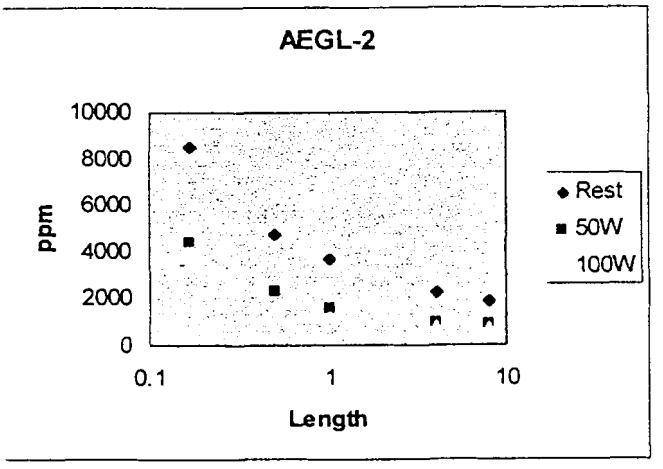
Effect of work on Cv:

Comparison of C_V at rest and at 50W. Curve above each label is 50W and curve below each label is at rest. Model run as before, changing QPC, QCC, and tissue flows per the table on previous slide. Resting conditions based on Gargas parameter set (0.55 QRC, 0.08 QFC, and 32 PB)



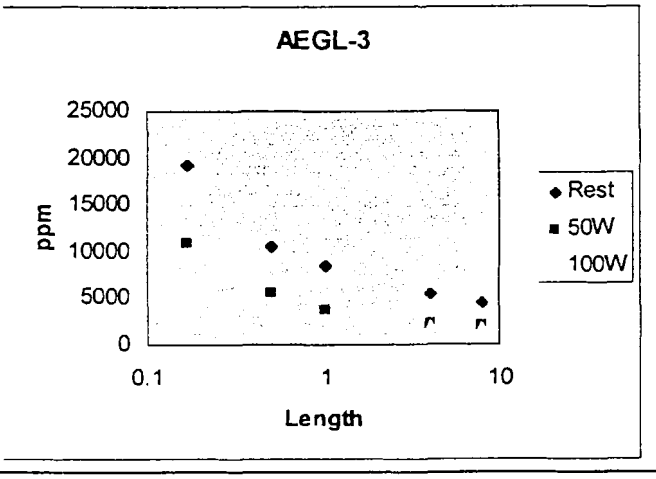
AEGL-2 values computed from the model as specified. Resting values are the average values.

Length	Rest	50W	100W
0.167	8525	4437	3450
0.5	4700	2320	1675
1	3715	1555	1166
4	2288	955	832
8	1867	870	767

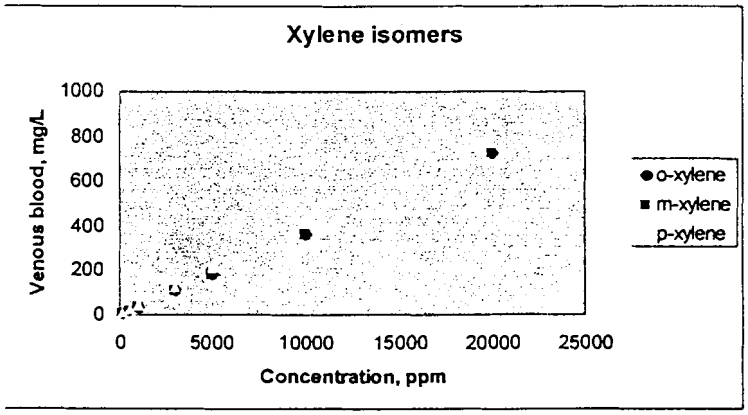


AEGL-3 values computed from the model as specified. Resting values are the average values.

Length	Rest	50W	100W
0.167	19100	10870	8453
0.5	10525	5664	4134
1	8400	3780	2842
4	5465	2305	2121
8	4472.5	2095	1862



Plot comparing the predicted Cv following exposure to individual isomers:



SUMMARY OF AEGL-2 VALUES					
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
NOMEN					
Mean	1165	570	-	-	-
-2 SD	985	483	(430)	(430)	(430)
-3 SD	896	438	-	-	-
PBPK					
Low	7300	4100	3300	2000	1700
Avg	8500	4700	3700	2300	1900
Avg/UF3	2800	1600	1200	760	620
PBPK with 50W work					
Avg	4400	2300	1600	960	870
Avg/UF3	1479	770	520	320	290

SUMMARY OF AEGL-3 VALUES					
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
NOMEN					
Mean	2500	1200	-	-	-
-2 SD	2100	1000	(930)	(930)	(930)
-3 SD	1800	960	-	-	-
PBPK					
Low	17,600	9850	7800	4800	3970
Avg	19,100	10,500	8400	5500	4500
Avg/UF3	6400	3500	2800	1800	1500
PBPK with 50W work					
Avg	10,900	5700	3800	2300	2100
Avg/UF3	3600	1900	1300	770	700

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Glossary of PBPK Model Terms:

Most used in the presentation:
Cv = venous blood concentration
PB = Blood/air partition coefficient

Physiological parameters

BW = Body weight (kg)
QPC = Alveolar ventilation rate (l/hr/kg)
QCC = Cardiac output (l/hr/kg)
VFC = Fraction fat tissue (kg/(kg/BW))
VLC = Fraction liver tissue (kg/(kg/BW))
VRC = Fraction rapidly perfused (kg/(kg/BW))
QFC = Fractional blood flow to fat ((l/hr)/QC)
QLC = Fractional blood flow to liver ((l/hr)/QC)
QRC= Fractional blood flow to rapidly perfused ((l/hr)/QC)
SF = Scaling coefficent

Chemical-specific parameters

PLA = Liver/air partition coefficient
PFA = Fat/air partition coefficient
PSA = Slowly perfused/air partition coefficient
PRA = Rapidly/air partition coefficient
PB = Blood/air partition coefficient
PL=PLA/PB Liver/blood partition coefficient
PF=PFA/PB Fat/blood partition coefficient
PS=PSA/PB Slowly perfused/blood partition coefficient
PR=PRA/PB Rapidly/blood partition coefficient

MW = Molecular weight (g/mol)
VMAXC = Maximum velocity of metabolism (mg/hr/kg)
KM = Michaelis-Menten (mg/l)
KFC = 0.1
CONC = Inhaled concentration (ppm)

Calculated parameters:

QC = QCC*BW^SF	Cardiac output
QP = QPC*BW^SF	Alveolar vent
VS = VSC*BW	Volume slowly perfused tissue (l)
VF = VFC*BW	Volume fat tissue (l)
VL = VLC*BW	Volume liver (l)
VR= VRC*BW	Volume rapidly perfused (l)
QF = QFC*QC	Blood flow to fat (l/hr)
QL = QLC*QC	Blood flow to liver (l/hr)
QS = QC - QF - QL - QR	Blood flow to non-fat tissue (l/hr)
QR = QRC*QC	Blood flow to rapidly perfused (l/hr)
CIX = CONC*MW/24450	Exposure concentration (mg/l)
VMAX = VMAXC*BW^SF	
KF = KFC/BW^0.3	1st order rate constant for high-capacity/low affinity enzymes